General

Guideline Title

Drug allergy: diagnosis and management of drug allergy in adults, children and young people.

Bibliographic Source(s)

National Clinical Guideline Centre. Drug allergy: diagnosis and management of drug allergy in adults, children and young people. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Sep. 36 p. (Clinical guideline; no. 183).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse: This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

The wording used in the recommendations in this guideline (for example, words such as 'offer' and 'consider') denotes the certainty with which the recommendation is made (the strength of the recommendation) and is defined at the end of the "Major Recommendations" field.

Assessment

When assessing a person presenting with possible drug allergy, take a history and undertake a clinical examination. Use the following boxes as a guide when deciding whether to suspect drug allergy.

Boxes 1–3. Signs and Allergic Patterns of Suspected Drug Allergy with Timing of Onset*

Box 1. Immediate, Rapidly Evolving Reactions

Anaphylaxis – a severe multi-system reaction characterised by: • Erythema, urticaria or angioedema and • Hypotension and/or bronchospasm	Onset usually less than 1 hour after drug exposure (previous exposure not always confirmed)
Urticaria or angioedema without systemic features	

Exacerbation of asthma (for example, with non-steroidal anti-inflammatory drugs [NSAIDs])	

Box 2. Non-immediate Reactions without Systemic Involvement

Widespread red macules or papules (exanthema-like)	Onset usually 6–10 days after first drug exposure or within 3 days of second exposure
Fixed drug eruption (localised inflamed skin)	

Box 3. Non-immediate Reactions with Systemic Involvement

Drug reaction with eosinophilia and systemic symptoms (DRESS) or drug hypersensitivity syndrome (DHS) characterised by: • Widespread red macules, papules or erythroderma • Fever • Lymphadenopathy • Liver dysfunction • Eosinophilia	Onset usually 2–6 weeks after first drug exposure or within 3 days of second exposure
Toxic epidermal necrolysis or Stevens–Johnson syndrome characterised by: • Painful rash and fever (often early signs) • Mucosal or cutaneous erosions • Vesicles, blistering or epidermal detachment • Red purpuric macules or erythema multiforme	Onset usually 7–14 days after first drug exposure or within 3 days of second exposure
Acute generalised exanthematous pustulosis (AGEP) characterised by: • Widespread pustules • Fever • Neutrophilia	Onset usually 3–5 days after first drug exposure
Common disorders caused, rarely, by drug allergy: • Eczema • Hepatitis • Nephritis • Photosensitivity • Vasculitis	Time of onset variable

*Note that these boxes describe common and important presenting features of drug allergy but other presentations are also recognised.

Be aware that the reaction is more likely to be caused by drug allergy if it occurred during or after use of the drug and:

- The drug is known to cause that type of reaction or
- The person has previously had a similar reaction to that drug or drug class.

Be aware that the reaction is less likely to be caused by drug allergy if:

- There is a possible non-drug cause for the person's symptoms (for example, they have had similar symptoms when not taking the drug) or
- The person has gastrointestinal symptoms only.

Measuring Serum Tryptase after Suspected Anaphylaxis

After a suspected drug-related anaphylactic reaction, take 2 blood samples for mast cell tryptase in line with recommendations in the NICE guideline Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode (NICE clinical guideline 134).

Record the exact timing of both blood samples taken for mast cell tryptase:

- In the person's medical records and
- On the pathology request form

Ensure that tryptase sampling tubes are included in emergency anaphylaxis kits.

Measuring Serum Specific Immunoglobulin E

Do not use blood testing for serum specific immunoglobulin E (IgE) to diagnose drug allergy in a non-specialist setting.

Documenting and Sharing Information with Other Healthcare Professionals

Recording Drug Allergy Status

Document people's drug allergy status in their medical records using one of the following:

- 'Drug allergy'
- 'None known'
- 'Unable to ascertain' (document it as soon as the information is available)

If drug allergy status has been documented, record all of the following at a minimum:

- The drug name
- The signs, symptoms and severity of the reaction (see boxes above)
- The date when the reaction occurred

Documenting New Suspected Drug Allergic Reactions

When a person presents with suspected drug allergy, document their reaction in a structured approach that includes:

- The generic and proprietary name of the drug or drugs suspected to have caused the reaction, including the strength and formulation
- A description of the reaction (see boxes above)
- The indication for the drug being taken (if there is no clinical diagnosis, describe the illness)
- The date and time of the reaction
- The number of doses taken or number of days on the drug before onset of the reaction
- The route of administration
- Which drugs or drug classes to avoid in future

Maintaining and Sharing Drug Allergy Information

Prescriptions (paper or electronic) issued in any healthcare setting should be standardised and redesigned to record information on which drugs or drug classes to avoid to reduce the risk of drug allergy.

Ensure that drug allergy status is documented separately from adverse drug reactions and that it is clearly visible to all healthcare professionals who are prescribing drugs.

Check a person's drug allergy status and confirm it with them (or their family members or carers as appropriate) before prescribing, dispensing or administering any drug (see "Providing Information and Support to Patients" below). Update the person's medical records or inform their general practitioner (GP) if there is a change in drug allergy status.

Ensure that information about drug allergy status is updated and included in all:

- GP referral letters
- Hospital discharge letters

Carry out medicines reconciliation for people admitted to hospital in line with recommendations in Technical patient safety solutions for medicines reconciliation on admission of adults to hospital (NICE patient safety solutions guidance 1).

Documenting Information after Specialist Drug Allergy Investigations

For recommendations on referral to specialist services see "Non-specialist Management and Referral to Specialist Services," below.

After specialist drug allergy investigations, allergy specialists should document:

- The diagnosis, drug name and whether the person had an allergic or non-allergic reaction
- The investigations used to confirm or exclude the diagnosis
- Drugs or drug classes to avoid in future

Providing Information and Support to Patients

Discuss the person's suspected drug allergy with them (and their family members or carers as appropriate) and provide structured written information (see "Documenting New Suspected Drug Allergic Reactions," above). Record who provided the information and when.

Provide information in line with the recommendations in Patient experience in adult NHS services (NICE clinical guideline 138).

Ensure that the person (and their family members or carers as appropriate) is aware of the drugs or drug classes that they need to avoid, and advise them to check with a pharmacist before taking any over-the-counter preparations.

Advise people (and their family members or carers as appropriate) to carry information they are given about their drug allergy at all times and to share this whenever they visit a healthcare professional or are prescribed, dispensed or are about to be administered a drug.

Providing Information and Support to People Who Have Had Specialist Drug Allergy Investigations

For recommendations on referral to specialist services see section "Non-specialist Management and Referral to Specialist Services," below.

Allergy specialists should give the following written information to people who have undergone specialist drug allergy investigation:

- The diagnosis – whether they had an allergic or non-allergic reaction
- The drug name and a description of their reaction (see boxes above)
- The investigations used to confirm or exclude the diagnosis
- Drugs or drug classes to avoid in future
- Any safe alternative drugs that may be used

Explain to people in whom allergy to a drug or drug class has been excluded by specialist investigation that they can now take this drug or drug class safely and ensure that their medical records are updated.

Non-specialist Management and Referral to Specialist Services

General

If drug allergy is suspected:

- Consider stopping the drug suspected to have caused the allergic reaction and advising the person to avoid that drug in future.
- Treat the symptoms of the acute reaction if needed; send people with severe reactions to hospital.
- Document details of the suspected drug allergy in the person's medical records (see "Documenting New Suspected Drug Allergic Reactions" and "Maintaining and Sharing Drug Allergy Information" above).
- Provide the person with information (see "Providing Information and Support to Patients" above).

Refer people to a specialist drug allergy service if they have had:

- A suspected anaphylactic reaction (see the NICE guideline Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode [NICE clinical guideline 134]) or
- A severe non-immediate cutaneous reaction (for example, drug reaction with eosinophilia and systemic symptoms [DRESS], Stevens–Johnson syndrome, toxic epidermal necrolysis).

Non-steroidal Anti-inflammatory Drugs (Including Selective Cyclooxygenase 2 Inhibitors)

Explain to people with a suspected allergy to a non-selective non-steroidal anti-inflammatory drug (NSAID) (and their family members or carers as appropriate) that in future they need to avoid all non-selective NSAIDs, including over-the-counter preparations.

For people who have had a mild allergic reaction to a non-selective NSAID but need an anti-inflammatory:

- Discuss the benefits and risks of selective cyclooxygenase 2 (COX-2) inhibitors (including the low risk of drug allergy).
- Consider introducing a selective COX-2 inhibitor at the lowest starting dose with only a single dose on the first day.

Do not offer a selective COX-2 inhibitor to people in a non-specialist setting if they have had a severe reaction, such as anaphylaxis, severe angioedema or an asthmatic reaction, to a non-selective NSAID.

Refer people who need treatment with an NSAID to a specialist drug allergy service if they have had a suspected allergic reaction to an NSAID with symptoms such as anaphylaxis, severe angioedema or an asthmatic reaction.

Be aware that people with asthma who also have nasal polyps are likely to have NSAID-sensitive asthma unless they are known to have tolerated NSAIDs in the last 12 months.

Beta-lactam Antibiotics

Refer people with a suspected allergy to beta-lactam antibiotics to a specialist drug allergy service if they:

- Need treatment for a disease or condition that can only be treated by a beta-lactam antibiotic or
- Are likely to need beta-lactam antibiotics frequently in the future (for example, people with recurrent bacterial infections or immune deficiency).

Consider referring people to a specialist drug allergy service if they are not able to take beta-lactam antibiotics and at least 1 other class of antibiotic because of suspected allergy to these antibiotics.

Local Anaesthetics

Refer people to a specialist drug allergy service if they need a procedure involving a local anaesthetic that they are unable to have because of suspected allergy to local anaesthetics.

General Anaesthesia

Refer people to a specialist drug allergy service if they have had anaphylaxis or another suspected allergic reaction during or immediately after general anaesthesia.

Definitions:

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally 'must' (or 'must not') is used if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer…') are used when confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Clinical Algorithm(s)

An algorithm titled "Suspected Drug Allergy" is provided in the full version of the guideline (see the "Availability of Companion Documents" field).

A NICE care pathway titled "Drug Allergy Overview" is available from the National Institute for Health and Care Excellence (NICE) Web site .

Scope

Disease/Condition(s)

Drug allergy

Note: This guideline does not cover other allergies (for example food allergies), treatment of the acute phase including anaphylaxis, investigation of allergies to individual drugs or in specific populations (unless specified in the scope), or treatment of non-allergic adverse drug reactions.

Guideline Category

Counseling

Diagnosis

Evaluation

Management

Prevention

Clinical Specialty

Allergy and Immunology

Anesthesiology

Critical Care

Dentistry

Emergency Medicine

Family Practice

Internal Medicine

Nursing

Pediatrics

Pharmacology

Preventive Medicine

Surgery

Intended Users

Advanced Practice Nurses

Dentists

Emergency Medical Technicians/Paramedics

Hospitals

Nurses

Patients

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To offer best practice advice on the care of adults, children and young people with suspected or confirmed drug allergy

Target Population

Adults, children and young people with suspected or confirmed drug allergy

Interventions and Practices Considered

Diagnosis/Evaluation

1. History and clinical examination including signs and allergic patterns of suspected drug allergy with timing of onset
2. Measuring serum tryptase after suspected anaphylaxis
3. Measuring serum-specific immunoglobulin E (IgE; not recommended to diagnose drug allergy in a non-specialist setting)
4. Recording drug allergy status in medical records
5. Documenting new suspected drug allergic reactions
6. Maintaining and sharing drug allergy information
7. Documenting information after specialist drug allergy investigations

Management/Counseling

1. Providing information and support to patients about their drug allergies
2. Providing information and support to people who have had specialist drug allergy investigations
3. Non-specialist management and referral to specialist services
    - Stopping the suspected drug and advising the person to avoid the drug in future
    - Treating the acute reaction if needed
    - Documenting details of suspected drug allergy in the medical records
    - Referral to specialist drug allergy service, as appropriate
4. Considerations for suspected allergies to non-selective non-steroidal anti-inflammatory drugs (NSAIDs), beta-lactam antibiotics, local anaesthetics, and general anaesthesia

Major Outcomes Considered

- Mortality
- Medication errors
- Length of hospital stay
- Acute admission and/or readmission into secondary care
- Number of contacts with healthcare professional

- Inappropriate avoidance of drugs
- Health-related quality of life
- Test accuracy measures (sensitivity, specificity, positive/negative predictive value)
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Developing the Review Questions and Outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews; in a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy; and using population, presence or absence of factors under investigation (for example prognostic factors) and outcomes for prognostic reviews. The experience of information provision for people with suspected or confirmed drug allergies was reviewed using qualitative information to capture preferences and perceptions (including factors which improve or act as a barrier to optimal care).

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the Guideline Development Group (GDG). The review questions were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (see Appendix A in the full version of the guideline [see the "Availability of Companion Documents" field]).

A total of 11 review questions were identified (see Table 1 in the full version of the guideline).

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Searching for Evidence

Clinical Literature Search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE Guidelines Manual, 2012. Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English. All searches were conducted in MEDLINE, EMBASE, and The Cochrane Library. In additional CINAHL was used for the information and support review. All searches were updated on 10 January 2014. No papers published after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GDG members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix G in the full version of the guideline.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria. During the scoping stage, a search was conducted for guidelines and reports on the websites listed below from organisations relevant to the topic. Searching for unpublished literature was not undertaken. All references sent by stakeholders

were considered.

- Guidelines International Network database (http://www.g-i-n.net/)
- National Guideline Clearinghouse (http://www.guideline.gov/)
- National Institute for Health and Care Excellence (NICE) (http://www.nice.org.uk)
- National Institutes of Health Consensus Development Program (http://consensus.nih.gov/)
- NHS Evidence Search (http://www.evidence.nhs.uk/)
- British Society for Allergy & Clinical Immunology (BSACI) (http://www.bsaci.org/)
- American Academy of Allergy, Asthma & Immunology (AAAAI) (http://www.aaaai.org/home.aspx).

Health Economic Literature Search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to drug allergy in the National Health Service Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA) and the Health Economic Evaluations Database (HEED) with no date restrictions. Additionally, the search was run on MEDLINE and EMBASE using a specific economic filter, from 2011, to ensure recent publications that had not yet been indexed by the economic databases were identified. Studies published in languages other than English were not reviewed. For databases, where it was possible, searches were restricted to articles published in English.

The health economic search strategies are included in Appendix G in the full version of the guideline. All searches were updated on 15 January 2014. No papers published after this date were considered.

Evidence of Effectiveness

The evidence was reviewed following the steps shown schematically in Figure 1 in the full version of the guideline:

- Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C in the full version of the guideline).

A 20% sample of each of the above stages of the reviewing process was quality assured by a second reviewer to eliminate any potential of reviewer bias or error.

Inclusion and Exclusion Criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix C in the full version of the guideline. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix K in the full version of the guideline. The GDG was consulted about any uncertainty regarding inclusion or exclusion.

The guideline population was defined to be people with suspected or confirmed drug allergies. For some review questions, the review population was defined by the drug or drug class the person was allergic to (for example beta-lactam antibiotics, non-steroidal anti-inflammatories [NSAIDs], local anaesthetics or general anaesthetics in review questions 8 to 11 [see the full version of the guideline document]).

In the diagnostic chapter serum immunoglobulin E (IgE) testing was reviewed for a list of drugs that was prioritised by the GDG: amoxicillin, ampicillin, cofactor, chlorhexidine, morphine, penicillin G, penicillin V, and suxamethonium.

The diagnostic serum tryptase review was restricted to patients with signs and symptoms of anaphylaxis.

Even though the prognostic review (to examine if there were certain characteristics of people with an allergy to NSAIDs who could take selective cyclooxygenase-2 [COX-2] inhibitors) had identified specific characteristics as prognostic factors, studies that were not designed to directly address these factors were not excluded. Studies that investigated the safety of taking selective COX-2 inhibitors for people with an allergy to NSAIDs more generally were included as indirect evidence. These studies were then divided by the study population (people with asthma or people with cutaneous reactions) to address the prognostic aspect of the question. For details of the approach to this review please refer to Chapter 10 in the full version of the guideline.

Randomised trials, non-randomised trials, and observational studies (including diagnostic or prognostic studies) were included in the evidence reviews as appropriate.

Conference abstracts were not automatically excluded from the review but were initially assessed against the inclusion criteria and then further processed only if no other full publication was available for that review question, in which case the authors of the selected abstracts were contacted for further information. None of the reviews in this guideline included conference abstracts as part of the evidence.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

The review protocols are presented in Appendix C in the full version of the guideline.

Type of Studies

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. If the GDG believed RCT data were not appropriate or there was limited evidence from RCTs, well-conducted non-randomised studies were included. Please refer to Appendix C in the full version of the guideline for full details on the study design of studies selected for each review question. For example in the questions on referral to specialist drug allergy services it was decided to include non-randomised trials since randomisation might not always be possible or appropriate.

For the diagnostic reviews and the algorithm and probability score review, cross-sectional and retrospective studies were included. For prognostic reviews, prospective and retrospective cohort studies were included.

Where data from observational studies were included, the GDG decided that the results for each outcome should be presented separately for each study and meta-analysis was not conducted.

Evidence of Cost-effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost-effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost-effectiveness') rather than the total implementation cost. Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economists:

- Undertook a systematic review of the published economic literature
- Undertook new cost-effectiveness analysis in priority areas

Literature Review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies (see below for details).

Inclusion and Exclusion Criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (Appendix F in the NICE Guidelines Manual, 2012, and the health economics review protocol in Appendix C in the full version of the guideline).

When no relevant economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implications of the recommendations.

Number of Source Documents

The number of source documents identified for each topic and clinical question is provided in Appendices E and F in the full version of the guideline (see the "Availability of Companion Documents" field).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Overall Quality of Outcome Evidence in Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Level	Description
High	Further research is very unlikely to change confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Evidence of Effectiveness

The evidence was reviewed following the steps shown schematically in Figure 1 in the full version of the guideline:

- Relevant studies were critically appraised using the appropriate checklist as specified in the NICE Guidelines Manual, 2012 (see the "Availability of Companion Documents" field). For diagnostic questions, the QUADAS-2 checklist was followed (see Appendix F in the NICE Guidelines Manual, 2012).
- Key information was extracted on the study's methods, PICO (patient, intervention, comparison, outcome) factors and results. These were presented in summary tables (in each review chapter) and evidence tables (see Appendix H in the full version of the guideline [see the "Availability of Companion Documents" field]).
- Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in Guideline Development Group (GDG) meetings:
    - Randomised studies: data were meta-analysed where appropriate and reported in Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiles (for intervention reviews).
    - Observational studies: data were presented as a range of values in GRADE profiles.
    - Prognostic studies: data were presented as a range of values, usually in terms of the relative effect as reported by the authors.
    - Diagnostic studies were presented as measures of diagnostic test accuracy (sensitivity, specificity, positive and negative predictive value). Coupled values of sensitivity and specificity were summarised in paired (sensitivity and specificity side by side) forest plots to

allow visual comparison between different index tests and to investigate heterogeneity more effectively (given data were reported at the same thresholds).
- Qualitative studies: each study was summarised in a table where possible, otherwise presented in a narrative.

A 20% sample of each of the above stages of the reviewing process was quality assured by a second reviewer to eliminate any potential of reviewer bias or error.

Methods of Combining Clinical Studies

Data Synthesis for Intervention Reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes, such as number of patients being treated with alternative beta-lactam antibiotics, or number of patients with medication errors.

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation) were required for meta-analysis. Data for continuous outcomes (such as prescription errors) were analysed using an inverse variance method for pooling weighted mean differences and, where the studies had different scales, standardised mean differences were used. A generic inverse variance option in RevMan5 was used if any studies reported solely the summary statistics and 95% confidence interval (95% CI) or standard error; this included any hazard ratios reported. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics (p values or 95% CIs); meta-analysis was then undertaken for the mean difference and SE using the generic inverse variance method in RevMan5. When the only evidence was based on studies that summarised results by presenting medians (and interquartile ranges), or only p values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects. Consequently, aspects of quality assessment such as imprecision of effect could not be assessed for evidence of this type.

Statistical heterogeneity was assessed by visually examining the forest plots, and by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity). Where considerable heterogeneity was present, the guideline developers carried out predefined subgroup analyses for type of drug allergy and age group (children or adults).

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p values or 95% CIs were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in RevMan5. Where p values were reported as 'less than', a conservative approach was undertaken. For example, if p value was reported as '$p\leq0.001$', the calculations for standard deviations will be based on a p value of 0.001.

For interpretation of the binary outcome results, differences in the absolute event rate were calculated using the GRADEpro software, for the median event rate across the control arms of the individual studies in the meta-analysis. Absolute risk differences were presented in the GRADE profiles and in clinical summary of findings tables, for discussion with the GDG.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

Data Synthesis for Prognostic Factor Reviews

Odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs), with their 95% CIs for the effect of the pre-specified prognostic factors were extracted from the papers when reported. For the purpose of the review question on tolerance of selective cyclooxygenase-2 (COX-2) inhibitors, factors that indicated whether the drug was safe to prescribe regardless of prognostic factors were also noted, such as the type of allergic reaction and the rate of severe reactions in response to the selective COX-2 inhibitor.

Data Synthesis for Diagnostic Test Accuracy Reviews

Data and Outcomes

For the reviews of diagnostic test accuracy, a positive result on the index test was found if the patient had values of the measured quantity above a threshold value, and different thresholds could be used. Diagnostic test accuracy measures used in the analysis were: sensitivity, specificity, positive and negative predictive value. The threshold of a diagnostic test is defined as the value at which the test can best differentiate between those with and without the target condition (for instance different thresholds were used in the serum tryptase review) and, in practice, it varies amongst studies. For this guideline, sensitivity and specificity were considered equally important. A high sensitivity (true positives) of a test can pick up the

majority of the correct cases with drug allergy; conversely, a high specificity (true negatives) can correctly exclude people without drug allergy.

Data Synthesis

Coupled forest plots of sensitivity and specificity with their 95% CIs across studies (at various thresholds) were produced for each test, using RevMan5. In order to do this, 2×2 tables (the number of true positives, false positives, true negatives and false negatives) were directly taken from the study if given, or else were derived from raw data or calculated from the set of test accuracy statistics.

Heterogeneity or inconsistency amongst studies was visually inspected in the forest plots where appropriate (only when there were similar thresholds). A diagnostic meta-analysis was not carried out because studies were not homogenous enough to assume a single underlying level of sensitivity and specificity (due to differences in population, type of index test or reference standard).

Data Synthesis for Qualitative Study Review

Where possible a meta-synthesis was conducted to combine qualitative study results. The main aim of the synthesis of qualitative data was a description of the main topics that may influence the experience of care of the person with suspected or confirmed drug allergy or their parents or carers, rather than build new theories or reconceptualise the topic under review. Whenever studies identified a qualitative theme, this was extracted and the main characteristics were summarised. When all themes were extracted from studies, common concepts were categorised and tabulated. This included information on how many studies had identified this theme. A frequently identified theme may indicate an important issue for the review, but frequency of theme is not the only indicator of importance. Study type and population in qualitative research can differ widely meaning that themes that may only be identified by one or a few studies can provide important new information. Therefore for the purpose of the qualitative review in this guideline the categorisation of themes was exhaustive, that is all themes were accounted for in the synthesis. The GDG could then draw conclusions on the relative merits of each of the themes and how they may help in forming recommendations.

Data Synthesis for the Algorithm and Probability Score Review

The aim of this review was to summarise evidence on issues that clinicians need to consider when assessing a person with a suspected drug allergy and the signs and symptoms that the person would present with. Assessments should be suitable for the primary care setting. It was decided that this topic would be best addressed with a review of already published assessment methods (that is, algorithms and probability scores) because of the multitude of individual features that may indicate a potential drug allergy. After a top-level search on this topic a published systematic review was identified. This review was edited (studies restricted to adverse drug events without drug allergies were excluded) and updated. For a full description of this specific data synthesis approach please see Chapter 5 in the full version of the guideline.

Data Synthesis for the Documentation Review

The aim of this review was to summarise evidence on the effectiveness of documentation strategies in preventing people with suspected or confirmed allergies receiving the drug they are allergic to. Study types considered for this review were randomised trials, and systematic reviews. Prospective and retrospective cohort studies, before and after studies, case series, surveys and qualitative studies were also considered, with the caveat that if a lot of evidence was identified for a particular documentation intervention then only the higher-level evidence be included in the review.

Due to the multitude of populations, study designs, interventions and reported outcomes an exception was made to the usual effectiveness reviews described above. The following approach was used:

- Evidence was classified according to the broad documentation category (for example, computerised systems or structured charts).
- Features of different documentation categories were then extracted.
- Outcomes (such as prescribing errors or alerts that were overwritten) were summarised and where possible related to the features of the documentation strategy.
- Study quality was assessed individually and then by the majority of evidence for a particular intervention and outcome.
- Overall quality was then assessed by documentation category.

Further details of this approach are described in Chapter 8 in the full version of the guideline.

Appraising the Quality of Evidence by Outcomes

The evidence for outcomes from the included RCTs and, where appropriate, observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results.

Results were presented in GRADE profiles ('GRADE tables'), which consist of 2 sections: the 'Clinical evidence profile' table includes details of the quality assessment while the 'Clinical evidence summary of findings' table includes pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the 'Clinical evidence profile' table if it was apparent.

The evidence for each outcome was examined separately for the quality elements listed and defined in Table 2 in the full version of the guideline. Each element was graded using the quality levels listed in Table 3 in the full version of the guideline. The main criteria considered in the rating of these elements are discussed below. Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (see the "Rating Scheme for the Strength of the Evidence" field).

The GRADE toolbox is currently designed only for randomised trials and observational studies but the GDG adapted the quality assessment elements and outcome presentation for diagnostic accuracy studies.

Grading the Quality of Clinical Evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start as High, observational studies as Low, and uncontrolled case series as Low or Very low.
2. The rating was then downgraded for the specified criteria: risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed in the full version of the guideline. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was: a large magnitude of effect, a dose–response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated down by 1 or 2 points respectively.
3. The downgraded or upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as High and the overall quality became Moderate, Low or Very low if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of the criteria used for each of the main quality element are discussed further in Sections 3.3.6 to 3.3.9 in the full version of the guideline.

Evidence Statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- The number of studies and the number of participants for a particular outcome
- A brief description of the participants
- An indication of the direction of effect (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments)
- A description of the overall quality of evidence (GRADE overall quality)

Evidence of Cost-effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost-effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost-effectiveness') rather than the total implementation cost. Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economists:

- Undertook a systematic review of the published economic literature
- Undertook new cost-effectiveness analysis in priority areas

Literature Review

The health economist:

- Critically appraised relevant studies using the economic evaluations checklist as specified in the NICE Guidelines Manual, 2012 (see the "Availability of Companion Documents" field).
- Extracted key information about the studies' methods and results into evidence tables (included in Appendix I in the full version of the guideline [see the "Availability of Companion Documents" field]).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter for each review question) – see below for details

NICE Economic Evidence Profiles

When relevant economic studies are identified a NICE economic evidence profile is used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows an assessment of applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments are made by the health economist using the economic evaluation checklist from the NICE Guidelines Manual, 2012. It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty in the analysis. See Table 6 in the full version of the guideline for more details.

If a non-UK study is included in the profile, the results are converted into pounds sterling using the appropriate purchasing power parity.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

A multidisciplinary Guideline Development Group (GDG) comprising health professionals and researchers as well as lay members developed this guideline. The GDG was convened by the NCGC and chaired by Dr Shuaib Nasser in accordance with guidance from NICE. The group met every 5 to 6 weeks during the development of the guideline. Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

Developing Recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices H and I of the full version of the guideline (see the "Availability of Companion Documents" field).
- Summaries of clinical and economic evidence and quality (as presented in Chapters 5–11 in the full version of the guideline)
- Forest plots (see Appendix J in the full version of the guideline)

Recommendations were drafted on the basis of the GDG's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the GDG took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the GDG's values and preferences), and the confidence the GDG had in the evidence (evidence quality). Secondly, whether the net benefit justified any differences in costs was assessed.

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion.

The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the GDG. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see Section 3.5.1 in the full version of the guideline).

The GDG considered the 'strength' of recommendations. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the GDG believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the GDG has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients.

The GDG focused on the following factors in agreeing the wording of the recommendations:

- The actions health professionals need to take
- The information readers need to know
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations)
- The involvement of patients (and their carers if needed) in decisions on treatment and care
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see Section 9.3 in "The Guidelines Manual" [2012] [see the "Availability of Companion Documents" field])

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter of the full version of the guideline.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally 'must' (or 'must not') is used if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer…') are used when confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Cost Analysis

Undertaking New Health Economic Analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economists in selected areas. Priority areas for new health economic analysis were agreed by the Guideline Development Group (GDG) after formation of the review questions and consideration of the available health economic evidence.

The GDG identified referral to specialist drug allergy services or alternative management strategies within primary care for patients who are not referred as the highest priority area for original economic analysis. The GDG believed that economic modelling in this area would be informative if feasible, but concluded that modelling was unfortunately not feasible as information was not available on the relative effectiveness of referral or non-specialist management on outcomes such as the number of future allergic reactions or the number of occasions alternative drugs are used. This was due both to the fact that as specialist management is outside the scope of this guideline the referral pathway is undefined, and to the lack of applicable published economic research on the areas that are within the scope. Therefore any model would necessarily have to be built largely upon estimates and assumptions. In particular, sufficient data were not available to allow modelling of different subgroups, which would be necessary to identify which individuals should or should not be referred to specialist drug allergy services.

Instead of conducting a full economic evaluation, four cost-effectiveness scenarios were constructed for the case of suspected allergy to beta-lactam antibiotics. These calculated the potential costs of both referral to specialist drug allergy services and of non-specialist management for multiple frequencies of future need for antibiotics. They presented the magnitude of difference in quality of life (measured in quality-adjusted life years [QALYs] or life days [QALDs]) which referral would need to be expected to yield for it to be cost effective compared to non-specialist management. The GDG used these scenarios to inform their recommendations regarding which people should and should not be referred to specialist drug allergy services.

The following general principles were adhered to in developing the cost-effectiveness scenarios:

- Methods were consistent with the National Institute for Health and Care Excellence (NICE) reference case.
- The GDG was involved in the design of the scenarios, selection of conditions and drugs examined and interpretation of the results.
- Costs were based on routine National Health Service (NHS) data sources.
- Inputs and assumptions were reported fully and transparently, and their limitations were discussed.

Full methods for the cost-effectiveness scenarios for referral to specialist drug allergy services are described in Chapter 11 in the full version of the guideline (see the "Availability of Companion Documents" field).

Cost-effectiveness Criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.

When QALYs or life years gained are not used in an analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

In the Absence of Economic Evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the National Institute for Health and Care Excellence (NICE) website.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis and management of drug allergy in adults, children and young people

See the "Trade-off between clinical benefits and harms" sections in the full version of the guideline (see the "Availability of Companion Documents" field) for details about benefits of specific interventions.

Potential Harms

- In the opinion of the Guideline Development Group's (GDG), the key potential harm of recommending the use of an algorithm to people with a suspected drug allergy is the poor predictive value provided by algorithms. Specifically, the lack of absolute prediction of whether the person presenting with a suspected drug allergy is experiencing an allergic reaction or not and the risk of clinicians providing false reassurance was a key concern. The GDG noted that signs and symptoms of drug allergy in children may differ from those in adults, and typical patterns suggesting an allergic reaction to a drug may not apply in a child's case. For example, non-specific rashes are more common in children and these are usually not due to drug allergy, whilst severe cutaneous reactions are less common in children. The GDG also recognised that people of certain ethnicities and those with certain comorbidities such as cystic fibrosis or human immunodeficiency virus (HIV) are at higher risk of allergic reaction to specific drugs or drug classes.
- The evidence indicated that the proportion of people who have anaphylactic reactions when they tested positive (positive predictive values [PPV]) was high. Specificity values were also generally very high (between 89% and 100%). However since sensitivity was variable and modest, many people without elevated levels of tryptase did have anaphylactic reactions due to drug allergy. They would therefore be missed at this time point and might receive the drug again in the future before referral to specialists. Moreover, people with negative tryptase results might wrongly believe that the reaction was unrelated to the drug they had received.

See the "Trade-off between clinical benefits and harms" sections in the full version of the guideline (see the "Availability of Companion Documents" field) for details about harms of specific interventions.

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute for Health and Care Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical

judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summaries of product characteristics of any drugs.

- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.
- Patients and healthcare professionals have rights and responsibilities as set out in the National Health Service (NHS) Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If the patient is under 16, their family or carers should also be given information and support to help the child or young person to make decisions about their treatment. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards.
- NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.
- If a young person is moving between paediatric and adult services, care should be planned and managed according to the best practice guidance described in the Department of Health's Transition: getting it right for young people.
- Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with drug allergies. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.
- For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also "Patient-centred Care" in the original guideline document).
- Be aware of or suspect abuse as a contributory factor to or cause of the symptoms or signs of drug allergy in children. Abuse may also coexist with drug allergy. See the NICE guideline on child maltreatment for clinical features that may be associated with maltreatment.
- The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

Implementation of the Guideline

Description of Implementation Strategy

The National Institute for Health and Care Excellence (NICE) has developed tools and resources to help organisations implement this guidance. These are available on the NICE Web site (see also the "Availability of Companion Documents" field).

Key Priorities for Implementation

The following recommendations have been identified as priorities for implementation.

Assessment

When assessing a person presenting with possible drug allergy, take a history and undertake a clinical examination. Use the following boxes as a guide when deciding whether to suspect drug allergy.

Boxes 1–3. Signs and Allergic Patterns of Suspected Drug Allergy with Timing of Onset*

Box 1. Immediate, Rapidly Evolving Reactions

Anaphylaxis – a severe multi-system reaction characterised by: • Erythema, urticaria or angioedema and	Onset usually less than 1 hour after drug exposure (previous exposure not always confirmed)

• Hypotension and/or bronchospasm	
Urticaria or angioedema without systemic features	
Exacerbation of asthma (for example, with non-steroidal anti-inflammatory drugs [NSAIDs])	

Box 2. Non-immediate Reactions without Systemic Involvement

Widespread red macules or papules (exanthema-like)	Onset usually 6–10 days after first drug exposure or within 3 days of second exposure
Fixed drug eruption (localised inflamed skin)	

Box 3. Non-immediate Reactions with Systemic Involvement

Drug reaction with eosinophilia and systemic symptoms (DRESS) or drug hypersensitivity syndrome (DHS) characterised by: • Widespread red macules, papules or erythroderma • Fever • Lymphadenopathy • Liver dysfunction • Eosinophilia	Onset usually 2–6 weeks after first drug exposure or within 3 days of second exposure
Toxic epidermal necrolysis or Stevens–Johnson syndrome characterised by: • Painful rash and fever (often early signs) • Mucosal or cutaneous erosions • Vesicles, blistering or epidermal detachment • Red purpuric macules or erythema multiforme	Onset usually 7–14 days after first drug exposure or within 3 days of second exposure
Acute generalised exanthematous pustulosis (AGEP) characterised by: • Widespread pustules • Fever • Neutrophilia	Onset usually 3–5 days after first drug exposure
Common disorders caused, rarely, by drug allergy: • Eczema • Hepatitis • Nephritis • Photosensitivity • Vasculitis	Time of onset variable

*Note that these boxes describe common and important presenting features of drug allergy but other presentations are also recognised.

Documenting and Sharing Information with Other Healthcare Professionals

Documenting New Suspected Drug Allergic Reactions

When a person presents with suspected drug allergy, document their reaction in a structured approach that includes:

- The generic and proprietary name of the drug or drugs suspected to have caused the reaction, including the strength and formulation
- A description of the reaction (see boxes above)
- The indication for the drug being taken (if there is no clinical diagnosis, describe the illness)
- The date and time of the reaction
- The number of doses taken or number of days on the drug before onset of the reaction
- The route of administration

- Which drugs or drug classes to avoid in future

Maintaining and Sharing Drug Allergy Information

Prescriptions (paper or electronic) issued in any healthcare setting should be standardised and redesigned to record information on which drugs or drug classes to avoid to reduce the risk of drug allergy.

Check a person's drug allergy status and confirm it with them (or their family members or carers as appropriate) before prescribing, dispensing or administering any drug (see "Providing Information and Support to Patients" below). Update the person's medical records or inform their general practitioner (GP) if there is a change in drug allergy status.

Providing Information and Support to Patients

Discuss the person's suspected drug allergy with them (and their family members or carers as appropriate) and provide structured written information (see "Documenting New Suspected Drug Allergic Reactions" above). Record who provided the information and when.

Ensure that the person (and their family members or carers as appropriate) is aware of the drugs or drug classes that they need to avoid, and advise them to check with a pharmacist before taking any over-the-counter preparations.

Providing Information and Support to People Who Have Had Specialist Drug Allergy Investigations

Allergy specialists should give the following written information to people who have undergone specialist drug allergy investigation:

- The diagnosis – whether they had an allergic or non-allergic reaction
- The drug name and a description of their reaction (see boxes above)
- The investigations used to confirm or exclude the diagnosis
- Drugs or drug classes to avoid in future
- Any safe alternative drugs that may be used

Non-specialist Management and Referral to Specialist Services

General

Refer people to a specialist drug allergy service if they have had:

- A suspected anaphylactic reaction (see the NICE guideline Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode [NICE clinical guideline 134]) or
- A severe non-immediate cutaneous reaction (for example, drug reaction with eosinophilia and systemic symptoms [DRESS], Stevens–Johnson syndrome, toxic epidermal necrolysis).

Non-steroidal Anti-inflammatory Drugs (Including Selective Cyclooxygenase 2 Inhibitors)

For people who have had a mild allergic reaction to a non-selective non-steroidal anti-inflammatory drug (NSAID) but need an anti-inflammatory:

- Discuss the benefits and risks of selective cyclooxygenase 2 (COX-2) inhibitors (including the low risk of drug allergy).
- Consider introducing a selective COX-2 inhibitor at the lowest starting dose with only a single dose on the first day.

Beta-lactam Antibiotics

Refer people with a suspected allergy to beta-lactam antibiotics to a specialist drug allergy service if they:

- Need treatment for a disease or condition that can only be treated by a beta-lactam antibiotic or
- Are likely to need beta-lactam antibiotics frequently in the future (for example, people with recurrent bacterial infections or immune deficiency).

General Anaesthesia

Refer people to a specialist drug allergy service if they have had anaphylaxis or another suspected allergic reaction during or immediately after general anaesthesia.

Implementation Tools

Audit Criteria/Indicators

Clinical Algorithm

Foreign Language Translations

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Safety

Timeliness

Identifying Information and Availability

Bibliographic Source(s)

National Clinical Guideline Centre. Drug allergy: diagnosis and management of drug allergy in adults, children and young people. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Sep. 36 p. (Clinical guideline; no. 183).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

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Guideline Developer(s)

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National Institute for Health and Care Excellence (NICE)

Guideline Committee

Guideline Development Group

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

At the start of the guideline development process all Guideline Development Group (GDG) members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest. Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B in the full version of the guideline (see the "Availability of Companion Documents" field).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Drug allergy: diagnosis and management of drug allergy in adults, children and young people. Full guideline. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Apr. 165 p. (Clinical guideline; no. 183). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Drug allergy: diagnosis and management of drug allergy in adults, children and young people. Appendices. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Apr. 271 p. (Clinical guideline; no. 183). Electronic copies: Available from the NICE Web site .
- Drug allergy: diagnosis and management of drug allergy in adults, children and young people. Baseline assessment tool. London (UK): National Institute for Health and Care Excellence; 2014 Sep. (Clinical guideline; no. 183). Electronic copies: Available from the NICE Web

site .

- Drug allergy: diagnosis and management of drug allergy in adults, children and young people. Costing statement. London (UK): National Institute for Health and Care Excellence; 2014 Sep. 10 p. (Clinical guideline; no. 183). Electronic copies: Available from the NICE Web site .
- Drug allergy: diagnosis and management of drug allergy in adults, children and young people. Clinical audit tool. London (UK): National Institute for Health and Care Excellence; 2014 Sep. (Clinical guideline; no. 183). Electronic copies: Available from the NICE Web site .
- The guidelines manual 2012. London (UK): National Institute for Health and Care Excellence (NICE); 2012 Nov. Electronic copies: Available from the NICE Archive Web site .

Patient Resources

The following is available:

- Drug allergy: diagnosis and management of drug allergy in adults, children and young people. Information for the public. London (UK): National Institute for Health and Care Excellence; 2014 Sep. 8 p. (Clinical guideline; no. 183). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download as a Kindle or EPUB ebook from the NICE Web site . Also available in Welsh from the NICE Web site .

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